



VA ResearchCurrents

VA seeking proposals for research on military deployments

The Office of Research and Development of VA is seeking to fund new research on Gulf War illnesses and a wide range of other issues relating to the health effects of military deployment. The new solicitation will add to VA's existing portfolio of research on the topic.

Since 1994, VA, the Department of Defense (DoD) and the Department of Health and Human Services have spent \$213 million on 224 research projects relating to the effects of military deployment. VA plans to spend up to an additional \$20 million on this initiative by the end of fiscal 2004.

"This is not a new focus for us, but we want to remind our investigators of the importance of this issue and

reemphasize our continuing commitment to it," said acting chief research and development officer James F. Burris, MD. "VA has always considered military occupational and environmental exposures to be a high-priority research area."

So far, research has documented a nearly two-fold increase in the rate of amyotrophic lateral sclerosis (ALS) in Gulf War veterans, compared to non-deployed veterans of the same era. Studies have also confirmed increased rates of illnesses such as chronic fatigue, musculoskeletal problems, asthma, post-traumatic stress disorder, depression and memory problems. In clinical trials funded jointly by VA and the Department of Defense, antibiotics failed to improve these symptoms, but

exercise and cognitive behavioral therapy proved effective.

The new solicitation is aimed at addressing issues faced not only by Gulf War veterans, but by service members in any hazardous deployment. Examples are the recent actions in Bosnia and Afghanistan, and even Project SHAD, an operation in the 1960s and '70s designed to test the vulnerability of warships to chemical or biological attack and to develop countermeasures. The current specter of war in the Mideast underscores the urgent need for additional deployment research.

"Because of the increased frequency
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Update from Rehabilitation Research and Development...

Partnership with Mann Foundation will advance BION technology

By Mindy Aisen, MD, Director

Rehabilitation is both transforming and expanding as a science, where cutting edge micro- and nano-technology may, indeed, be the new assistive technology. This is why VA's Rehabilitation Research and Development Service (RR&D) is pleased to announce a new partnership with the Alfred E. Mann Foundation (AMF) to explore BION technology.

BIONs, a trademarked name from the words "bionic neurons," are wireless, implantable stimulating devices. This is an exciting opportunity to merge platform technology and clinical research to enhance the quality of rehabilitation and make available cutting-edge therapies to veterans.

AMF, a nonprofit corporation based in California, has made major technological contributions to numerous assistive devices and therapies, including Cochlear implants, neuromuscular stimulation, and long-life cardiac pacing systems. The Mann Foundation has a team of engineers and scientists with expertise in low-power subminiature integrated circuit design; digital and analog radio communications; mechanical engineering; implantable, rechargeable power source engineering; control and user interface software engineering; and system-level engineering.

BION technology is on the cusp of the man and machine

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Once-weekly drug regimen effective in tuberculosis trial

In a study published in the Aug. 17 issue of *The Lancet*, VA investigators and colleagues at 23 medical centers in the United States and Canada confirmed that a once-weekly tuberculosis (TB) regimen using the new long-acting drug rifapentine, initiated after the first two months of therapy, is a viable option for HIV-negative patients with no signs of advanced TB. The new regimen, compared to the standard twice-weekly regimen, may help improve adherence among TB patients and prevent further transmission of the disease.

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interface. A BION is a wireless and implantable microchip, about the size of a grain of rice, that is programmed externally. The microchip delivers digitally controlled and regulated pulses that interact with the muscular system, activating nerves. Significantly, BIONS, because of their size, can be implanted by injection in an outpatient setting by any physician, reducing clinical costs. They also have numerous benefits for the veteran population, including decreased risk of infection, skin breakdown or tissue damage.

BIONS hold the promise to improve functioning in veterans receiving health-care services for motor rehabilitation, bowel and bladder control, swallowing and vocal control difficulties, cardiorespiratory conditioning, pain management, and other conditions and diseases.

The cooperative research and development agreement (CRADA) with the Mann Foundation is one of the first agreements RR&D has signed outside of federal laboratories. AMF has technology and fabricating facilities with great potential for clinical application, but no clinical base. On the other hand, RR&D has an interest in advancing platform technology, but focuses its research and development efforts on studies with clinical relevance. Together, AMF and RR&D resources form a seamless transition from bench science to clinical research. Studies will be jointly managed and any intellectual property developed as a result of collaborative work will be shared.

Although the CRADA was signed only recently, the partnership is progressing well. A consensus meeting has been held and a request for proposals is about to be issued. We are expecting letters of intent in late January or early February. RR&D is also incorporating clinical applications of BION technology into research and development priorities. With this partnership and others that are currently under negotiation, RR&D continues to build the infrastructure necessary to lead rehabilitation research and ultimately to rewrite standards of rehabilitative care. ■

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of deployments, together with a downsizing of the active duty force, members of the armed forces are facing potentially hazardous environments with increasing regularity,” noted Kelley Ann Brix, MD, assistant chief research and development officer for VA.

The new program announcement identifies five major research categories as priorities:

- Long-term health effects of hazardous deployments
- Health impacts of specific military exposures
- Improvements in the diagnosis and evaluation of deployment-related illnesses
- Improvements in the treatment of deployment-related illnesses
- Health-risk communication for veterans and health-care providers.

All four of VA’s research services—Medical Research, Cooperative Studies, Rehabilitation Research, and Health Services—will be reviewing letters of intent submitted by VA investigators. The solicitation is open-ended, however proposals must be submitted by the application deadline of the relevant research service. Studies are especially encouraged that address gaps in existing research; that involve collaboration with DoD; and that would likely result in specific clinical or policy recommendations within a short time frame. The full program announcement, including extensive background, references, and instructions, can be found on the Web at <http://www.va.gov/resdev>. Click on “What’s New” under the “Research Programs” heading, and then click on “Program Announcement: Deployment Health Issues.” ■

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Study holds promise for safer hormone replacement therapy

A VA scientist has identified a synthetic estrogen-like compound that reverses bone loss in mice without the reproductive side effects associated with conventional hormone replacement therapy (HRT). The finding, reported in the Oct. 25 edition of *Science*, could lead to new therapies to prevent osteoporosis and enable safer alternatives to existing hormone treatments, shown earlier this year to pose more serious risks than previously thought.

“We are developing a new class of pharmaceutical agents with the potential for bone-building, sex-neutral hormone replacement therapy,” said lead investigator Stavros C. Manolagas, MD, PhD, an endocrinologist with the Central Arkansas Veterans Health Care System and the University of Arkansas for Medical Sciences.

Manolagas’ team reported last year in the journal *Cell* that sex hormones exert their bone-protecting and reproductive effects through separate cellular mechanisms. The researchers also identified a synthetic estrogen-like hormone—“estren”—that works in one pathway but not the other. The new study is the first time scientists have demonstrated in animals how synthetic hormones can work in this mode to build bone without affecting reproductive organs.

Manolagas and colleagues tested the effects of estren, compared to conventional estrogen and testosterone, in male and female mice. Some of the mice had their ovaries or testis removed, to halt the production of their natural sex hormones. The researchers then gave back a naturally occurring form of estrogen, for females, or testosterone, for males, to one group of sex-organ-deficient mice. Another group received the synthetic hormone estren, regardless of sex.

Remarkably, estren was even more effective than estrogen for females, and just as effective as testosterone for males, in helping bone. In fact, while estrogen only prevented bone loss, the estren actually increased bone density and strength, even to levels above those of the female mice with their ovaries intact.

Most important, the estren—unlike the estrogen or testosterone—had no effect on the weight of the uterus or seminal vesicle. Moreover, the estren, unlike estrogen, did not trigger the growth of breast-cancer cells in a Petri dish. While estrogen preserves the mass and function of female sex organs, it has also been shown to cause tumors with prolonged use as a therapy. ■

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The study was conducted by the Tuberculosis Trials Consortium, a project of the Centers for Disease Control (CDC). Participating in the study were 14 VA hospitals: San Antonio, Houston, Little Rock, Durham, Chicago (Lakeside, Hines and Westside), Los Angeles, San Francisco, Washington, DC; Nashville, Miami, New York and the Bronx.

In the trial, more than 1,000 HIV-negative patients with active TB disease completed eight weeks of intensive therapy with the four frontline TB drugs—isoniazid, rifampin, pyrazinamide and ethambutol—before being randomly assigned to one of two groups during the 16-week continuation phase of TB treatment.

The experimental group received isoniazid and rifapentine once a week. Rifapentine, the first new TB drug approved by the Food and Drug Administration since the 1970s, stays in the bloodstream longer than other TB drugs.

The control group received the standard therapy of twice-weekly isoniazid and rifampin.

Both groups of patients were followed for two years. Nine percent of those on the once-weekly regimen either relapsed or experienced treatment failure. Six percent on the twice-weekly regimen relapsed or had a treatment failure. However, when the study team reviewed data on those patients without lung cavities, they found that the relapse rates were comparable—about three percent in both treatment arms.

“We identified a group of HIV-negative patients in whom the once-a-week therapy would be as successful as other currently approved treatment regimens,” said team member Carol Dukes Hamilton, MD, of the Durham VA Medical Center and Duke University.

The CDC will be incorporating the once-weekly regimen into its new TB treatment guidelines, due out by early 2003. ■

Career achievements

Morris Weinberger, PhD, of the Institute for Clinical and Epidemiological Research at the Durham VA Medical Center, received the 2002 Vision Award from the organization “Improving Chronic Illness Care.” The group recognized Weinberger for his “innovative and methodologically rigorous research on methods to improve the care of patients with arthritis, diabetes, and other major chronic conditions.”

Hayden B. Bosworth, PhD, also of the Institute for Clinical and Epidemiological Research in Durham, received the Margaret M. Baltes Early Career Award from the Gerontological Society of America. The award is given for early-career contributions in clinical medicine and the biological, behavioral and social sciences. The award comes with an honorarium and an invitation to lecture at the Gerontological Society of America Fall 2003 meeting in San Diego.

Authors sought for history of VA research

Dr. Marguerite Hays, one-time head of VA research nationwide and today a consultant at the Palo Alto VA Medical Center, is seeking authors to help write a comprehensive history of VA research.

The book will contain two volumes. The first volume, penned by Hays herself—based on more than 200 firsthand interviews and a variety of other sources—chronicles VA research from its inception in 1925 through 1980. The second volume will contain chapters written by various authors and edited by Hays, detailing the history of specific subject areas in VA research or the history of research programs at individual medical centers.

While the book will certainly contain information about medical breakthroughs involving VA—such as the invention and first successful implantation of the cardiac pacemaker, at the Buffalo VAMC in 1960—Hays’ goal is to bring into the limelight more of the painstakingly incremental work that leads to such major advances.

“I want to talk about the journeymen people,” said Hays, whose research career has focused on nuclear medicine. “For every breakthrough that occurs, there are an awful lot of people doing the step-by-step research. That’s the real way in which science occurs. These people don’t always get the attention. I hope this book helps remedy that.”

If you are interested in contributing a chapter about your field of research or medical center, or would like more information, contact Hays at Ritahays19@yahoo.com or Marguerite.Hays2@med.va.gov. ■

For the date of VA R&D’s next National Hotline Conference Call, visit:

http://vawww.va.gov/resdev/fr/call_calendar.cfm

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